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Placement of Balloon-expandable Intraluminal Stents in Iliac Arteries: First 171 Procedures[1]

Balloon-expandable intraluminal stents were used to treat iliac artery stenoses or occlusions that failed to respond to conventional balloon angioplasty. One hundred seventy-one procedures were performed in 154 patients, of whom 48 had a limb at risk for amputation. Thirty-six had severe and 70 had moderate intermittent claudication. At the latest follow-up examination (average, 6 months; range, 1–24 months), 137 patients demonstrated clinical benefit, 113 of whom had become asymptomatic. Eleven patients showed no initial benefit, and six improved initially but later developed new vascular symptoms. Complications occurred in 18 patients. In three patients, complications were directly related to the device. Two occlusions were successfully recanalized, and an intramural collection of contrast material secondary to balloon perforation evolved favorably. The remaining patients had groin hematoma (n = 6), distal embolization (n = 4), extravasation (n = 2), transient renal failure (n = 1), pseudoaneurysm at the puncture site (n = 1), or subintimal dissection (n = 1). All stents have remained patent to the latest follow-up examination without evidence of migration or aneurysm formation.

Index terms: Arteries, extremities, 98.721 • Arteries, grafts and prostheses, 98.456 • Arteries, iliac, 98.721 • Arteries, stenosis or obstruction, 98.721 • Arteries, transluminal angioplasty, 98.128 • Arteriosclerosis, 98.721

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To determine the safety and efficacy of placement of balloon-expandable intraluminal stents as a treatment for subtotal or total occlusion of the iliac arteries, a multicenter clinical trial was instituted. This trial, approved by the U.S. Food and Drug Administration and the institutional review boards of the participating institutions, started in May 1987. The early results were encouraging and demonstrated an acceptably low complication rate (1). This warranted continuation of the study to allow accrual of a significantly large patient population and sufficiently long-term follow-up. These patients underwent implantation of the device under an experimental protocol and will be subject to lifelong scrutiny. The clinical and laboratory data obtained from the first 154 consecutive patients who underwent stent placement in symptomatic iliac artery lesions are the subject of this report.

MATERIALS AND METHODS

Study Population

The 154 patients were 28 women and 126 men with an average age of 62.7 years ± 10 (mean ± standard deviation [SD]) (range, 42–90 years). Atherosclerosis risk factors in this group included adult-onset diabetes mellitus (20.0%), cigarette smoking (96.1%), high blood pressure (52.2%), and obesity (17.2%). Forty-five percent of the patients had a history of coronary artery disease, and 15.1% had symptoms of cerebrovascular disease. Their peripheral vascular disease was graded into four stages: asymptomatic (stage I), lower-extremity intermittent claudication at more than 50 m (stage II), intermittent claudication at less than 50 m (stage III), and limb at risk for amputation, as defined by the presence of a nonhealing skin ulcer, gangrene, and/or ischemic pain at rest (stage IV). At presentation, 70 patients were in stage II, 36 in stage III, and 48 in stage IV (Fig 1). One hundred thirty-four patients had iliac artery stenoses, and 20 had complete iliac artery occlusion. Twelve of these patients were previously described (2). The average iliac artery stenosis was 79% ± 15% (mean ± SD) with an average length of 2.9 cm ± 2.6 (mean ± SD). The mean length of the iliac artery occlusions was 6.1 cm ± 2.8 (range, 1.4–12 cm). The average Doppler ankle-arm index of the symptomatic lower extremity was 0.63 ± 0.2 (mean ± SD) in stage II patients, 0.54 ± 0.17 in stage III patients, and 0.49 ± 0.25 in stage IV patients (Table).

Procedure

The device under evaluation, described in detail previously (1), is manufactured by Johnson & Johnson Interventional Systems (Warren, NJ). It consists of a slotted, seamless stainless steel tube 3.1 mm in diameter and 30 mm long, with a wall thickness of 0.015 mm (Fig 2). The stent is crimp-mounted on a folded, 8 × 30-mm angioplasty balloon catheter (PE Plus-II, USCI, Billerica, Mass) and placed into the stenotic area through a 10-F, 30-cm-long introducer sheath with a hemostatic valve (Cook, Bloomington, Ind). After the stent-balloon assembly is fluoroscopically positioned at the desired level, the sheath is withdrawn and the stent is deployed by inflation of the balloon (Fig 3).

Angiographic and hemodynamic assessment was performed after conventional balloon angioplasty to preclude stent placement in patients with good response to conventional angioplasty. Patients with inadequate response immediately after angioplasty underwent stent placement (Fig 4). Inadequate response to angioplasty was defined as the presence of intimal dissection or elastic recoil producing a residual luminal stenosis of 30% or more and/or a transstenotic mean pressure gradient of 5 mm Hg or more after injection of vasodilators distal to the

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treated segment. In patients in whom stents were placed, preliminary dilation decreased friction between the introducer sheath and the lesion and tested the distensibility of the stenotic area in order to preclude placing stents in an unyielding lesion.

Indications for stent placement were (*a*) inadequate immediate postangioplasty response as defined above, (*b*) restenosis after previous iliac balloon angioplasty (Fig 5), and (*c*) total iliac artery occlusion. Contraindications for stent placement included (*a*) extravasation of contrast material after balloon angioplasty, (*b*) markedly tortuous iliac arteries, and (*c*) dense, extensive arterial calcification. Concomitant iliac artery aneurysm, severe hypertension, impaired pain sensation, stenosis of the common femoral artery, and poor distal arterial outflow were considered relative contraindications, and precautionary measures were taken to prevent complications in such circumstances. These measures included drug control of hypertension, prevention of oversedation and prohibition of general anesthesia in patients with small, calcified, or aneurysmal iliac arteries, and liberal use of anticoagulants and vasodilators.

After a thorough explanation of the potential risks and benefits of the procedure, a signed informed consent was obtained from each patient. Premedication included oral aspirin (325 mg/d) and dipyridamole (25 mg every 8 hours), starting 48 hours before the procedure and continuing for 3 months thereafter. During the procedure, a total of 5,000–8,000 U of heparin were administered. Whenever a measurement of activated clotting time was available, it was maintained at 200–250 seconds. Whenever possible, the transstenotic pressure gradient was measured by means of simultaneous recording with two pressure transducers. One transducer was connected to a 5-F catheter with its tip placed at the aortic bifurcation, and the other was connected to the side arm of the introducer sheath. Otherwise, pressures were obtained sequentially, distal and proximal to the lesion, before and after stent placement, and before and after vasodilation. Serial angiograms were obtained after the initial balloon dilation and after stent placement. A guide wire was always maintained across the lesion during catheter exchanges. After achievement of hemostasis at the puncture site, the patient remained in bed for 12 hours and was then allowed bathroom privileges and limited mobility. The patient was discharged on the morning of the 3rd day.

Twelve patients underwent stent placement in addition to a surgical outflow procedure. Stent placement was done intraoperatively in seven patients, preoperatively in three patients, and shortly after surgery in two patients. The surgical procedures were femorofemoral bypass (four patients), reverse saphenous femoropopliteal bypass (three patients), reverse saphenous femorotibial bypass (one patient), and endarterectomy and profundaplasty (four patients). Ten of these combined procedures were performed in stage IV patients and two in stage III patients.

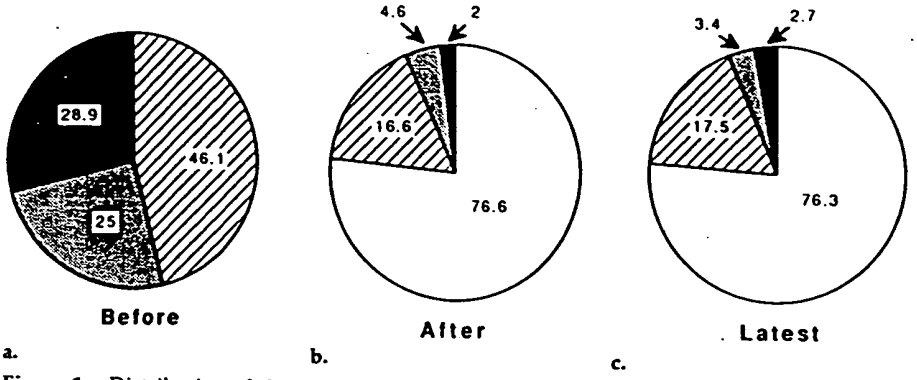

Figure 1. Distribution of clinical stages of ischemic peripheral vascular disease before treatment (a); at the first visit, usually within 2 weeks after discharge (b); and at the latest clinical follow-up (c). Black = limb at risk, gray = severe claudication, striped = moderate claudication, white = asymptomatic.

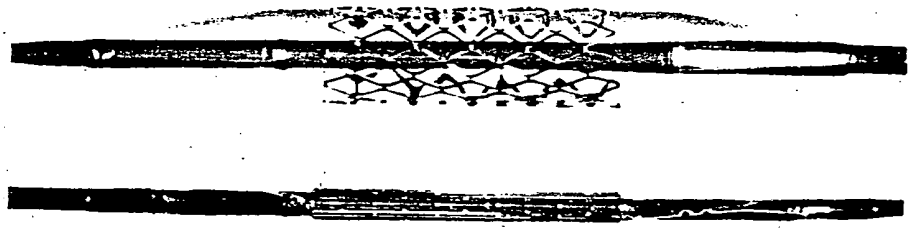

Figure 2. Mounted stent in expanded (top) and unexpanded states.

Effect on Treatment on Ankle-Arm Pressure Index

Stage	Ankle-Arm Index*		
	Before Treatment	After Treatment	Latest
II (n = 70)	0.63 ± 0.19	0.91 ± 0.22†	0.90 ± 0.20†
III (n = 36)	0.54 ± 0.17	0.83 ± 0.22†	0.85 ± 0.23†
IV (n = 48)	0.49 ± 0.25	0.75 ± 0.25†	0.84 ± 0.28†

* Mean ± SD.
† $P < .0001$.

Follow-up evaluation consisted of assessment of exercise tolerance, pulses, and segmental Doppler pressures at 2, 4, 12, and 24 weeks, and every 6 months thereafter. Follow-up also included a pelvic radiograph at 3 months and an aortoiliac angiogram at 6 months. The thickness of the tissue covering the inner surface of the vessel containing the stent was determined on the 6-month angiogram by measuring the difference in diameter between the radiopaque stent and the opacified lumen of the vessel segment. The following calculation was applied: Tissue Thickness = (Diameter of Stent − Diameter of Segment Lumen) ÷ 2.

Data evaluation.—Vascular disease staging before and after the procedure and at the latest follow-up was evaluated with χ^2 analysis. The level of significance was set at $P < .05$. Ankle-arm Doppler pressure ratios and intraarterial pressure data before and after stent placement were evaluated with the paired t test.

RESULTS

The 154 patients underwent 261 stent placements during 171 separate procedures. One hundred eighty-one stents were placed in common iliac arteries, and 80 stents were placed in external iliac arteries. Seventeen patients underwent bilateral stent placement, and 21 patients underwent stent placement in ipsilateral common and external iliac arteries. A

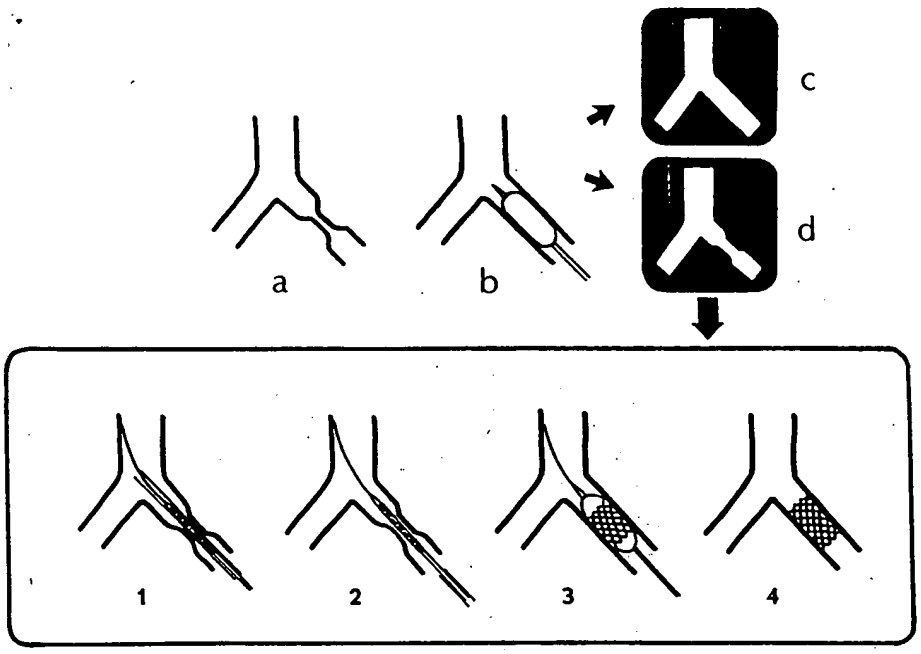

Figure 3. A stenotic iliac lesion (*a*) is first dilated with an angioplasty balloon (*b*). This may result in adequate result (*c*) or inadequate result (*d*). Angioplasty failures or eventual restenoses are subject to stent placement. (*1*) A balloon-mounted stent is advanced to the target through a sheath. (*2*) The sheath is withdrawn. (*3*) Balloon inflation simultaneously expands the stenotic lesion and the stent. (*4*) The stent maintains vessel patency after withdrawal of the balloon.

maximum of four stents were placed in a single iliac artery, and up to seven stents were placed in one patient.

The mean postvasodilation intraarterial pressure gradient as measured at the aortic bifurcation and distal external iliac artery prior to treatment was 36.4 mm Hg ± 22 (mean ± SD). Immediately after the procedure the gradient fell to 1.6 mm Hg ± 2.7 (P = .0001). Only five of the treated iliac arteries had a gradient of 10 mm Hg or greater after treatment.

At the first scheduled examination after the procedure, 114 patients were asymptomatic, 25 had moderate claudication, seven had severe claudication, four had healing skin lesions, and four were lost to follow-up (Fig 1). At the latest follow-up examination (average, 6 months; range, 1–24 months; 38.9% ≥ 1 year), 113 patients were asymptomatic, 25 had moderate claudication, five had severe claudication, two developed rest pain, and one had undergone below-the-knee amputation. Despite the apparent similarity in the composition of these groups, there was considerable crossover among the different clinical stage categories over this time because of either further vascular therapy or spontaneous change. The latest clinical examination showed net benefit in 134 patients (71 patients improved by one stage, 32 patients by two stages, and 31 patients by three stages; P = .001), no initial improvement in 11 patients, and initial improvement followed by new vascular symptoms in six patients. In this last group, two developed claudication in the opposite lower extremity, three developed rest pain, and one underwent an ipsilateral below-the-knee amputation for diabetic gangrene 3 months after stent placement.

At the early follow-up examination, those patients who initially had stage II disease had an increase in the ankle-arm Doppler pressure index on the symptomatic side to 0.91 ± 0.22 (mean ± SD); stage III patients increased to 0.83 ± 0.22, and stage IV patients increased to 0.75 ± 0.25. At the latest follow-up examination, the indexes were 0.90 ± 0.20, 0.85 ± 0.23, and 0.84 ± 0.28 for patients initially in stages II, III, and IV, respectively (Table).

Complications

Three patients (2%) developed complications directly attributable to the device. In two of these patients, thrombosis developed in the stent within a week of placement. In one, the thrombosis resulted from low flow, because the stent had been placed immediately cephalad to a stenotic area. This patient was previously described (1). The thrombus was lysed with intraarterial urokinase, and the stenosis was dilated with a balloon. This stent has remained patent during 1 year of follow-up. In the second patient, thrombosis developed in the stent without apparent hemodynamic impairment. However, this patient had systemic lupus erythematosus and Raynaud phenomenon and was being treated with systemic corticosteroids. The thrombosed stent was recanalized with fibrinolytic therapy and became thrombosed again on three separate occasions until an adequate level of anticoagulation was obtained with coumarin. The third patient developed a small intramural collection of contrast material at the level of the stent as a consequence of balloon perforation during expansion. Stent placement was completed with a new balloon. The collection evolved favorably as judged with computed tomographic scans.

Procedure-related complications occurred in 9.7% of patients. Six patients had groin hematomas that required transfusion or surgical evacuation. Four patients had peripheral embolization of organized, nonlysable material at the time of predilation with the angioplasty balloon; three of these occurred in patients with chronic total iliac occlusions 8, 9, and 12 cm long, respectively. The last two patients were previously described (2). All embolizations were treated successfully by means of surgical embolectomy. One patient had angiographic evidence of extravasation after the preliminary balloon dilation and did not receive a stent. In an additional patient minimal extravasation was noted at the tip of the introducer sheath; this was considered insignificant, and a stent was placed distal to it without adverse effect. One patient developed transient renal failure that responded favorably to conservative therapy. One patient developed a pseudoaneurysm at the puncture site. After preliminary balloon angioplasty, one patient developed subintimal dissection that extended cephalad into the aorta. After placement of three stents in the iliac artery, no further treatment was given and the patient remained asymptomatic.

At latest follow-up five patients had died. Two patients died of advanced metastatic cancer. One died of a perioperative myocardial infarction after femorofemoral bypass surgery 1 week after stent placement in the iliac artery opposite to the symptomatic lower extremity. Two additional patients died of fatal myocardial infarction 4 and 24 months, respec-

tively, after stent placement. A detailed histologic examination of one stent was made at the autopsy of the patient who died of metastatic cancer 2 months after the procedure. The patent stent was embedded in fibromuscular tissue averaging 0.22 mm in thickness, and evidence of resolving thrombus was seen around the stent struts (Fig 6).

Of the 125 patients who underwent 6 months of follow-up examinations after treatment, 43 agreed to undergo an aortoiliac angiographic study. In this group, the average intimal thickness of the segment with the stent was 0.79 mm ± 0.52 (mean ± SD). The patency rate of the stents at the latest follow-up examination, as determined by means of angiographic and/or clinical and hemodynamic evaluation, was 100%. This includes the two patients in whom the stents thrombosed and were recanalized. No evidence of stent migration or aneurysm formation has been seen.

Despite adequate counseling of patients, compliance with abstention from smoking was achieved in only 59.4% after treatment.

DISCUSSION

Despite general agreement as to the relative safety and immediate success of percutaneous iliac angioplasty, its long-term efficacy remains subject to debate. The reported clinical success at 1 year varies from 34% to more than 80% (3–6). This discrepancy is partially explained by variations in patient selection, persistence of major risk factors causing progression of the disease, and by the definition of success. Johnston et al (7) found that the presence of factors such as advanced disease (ie, limb salvage vs claudication), stenosis in the external as opposed to the common iliac artery, complete occlusion, and poor runoff negatively influenced the outcome of the procedure.

Hemodynamic improvement is recognized as a determinant of clinical improvement, and the success of surgical aortofemoral bypass is essentially based on the interposition of large, unobstructed conduits between the aorta and femoral arteries (4). Patients with aortoiliac occlusive disease commonly have atherosclerotic lesions in other locations as well. An average of 34% of these patients have significant coronary artery disease (8–10); in fact, up to 67% of all early postoperative deaths after aortofemoral bypass surgery are due to myocardial infarction (8). Percutaneous balloon angioplasty of obstructive aortoiliac disease has the potential to improve distal blood flow while lowering operational morbidity and mortality. Unfortunately,

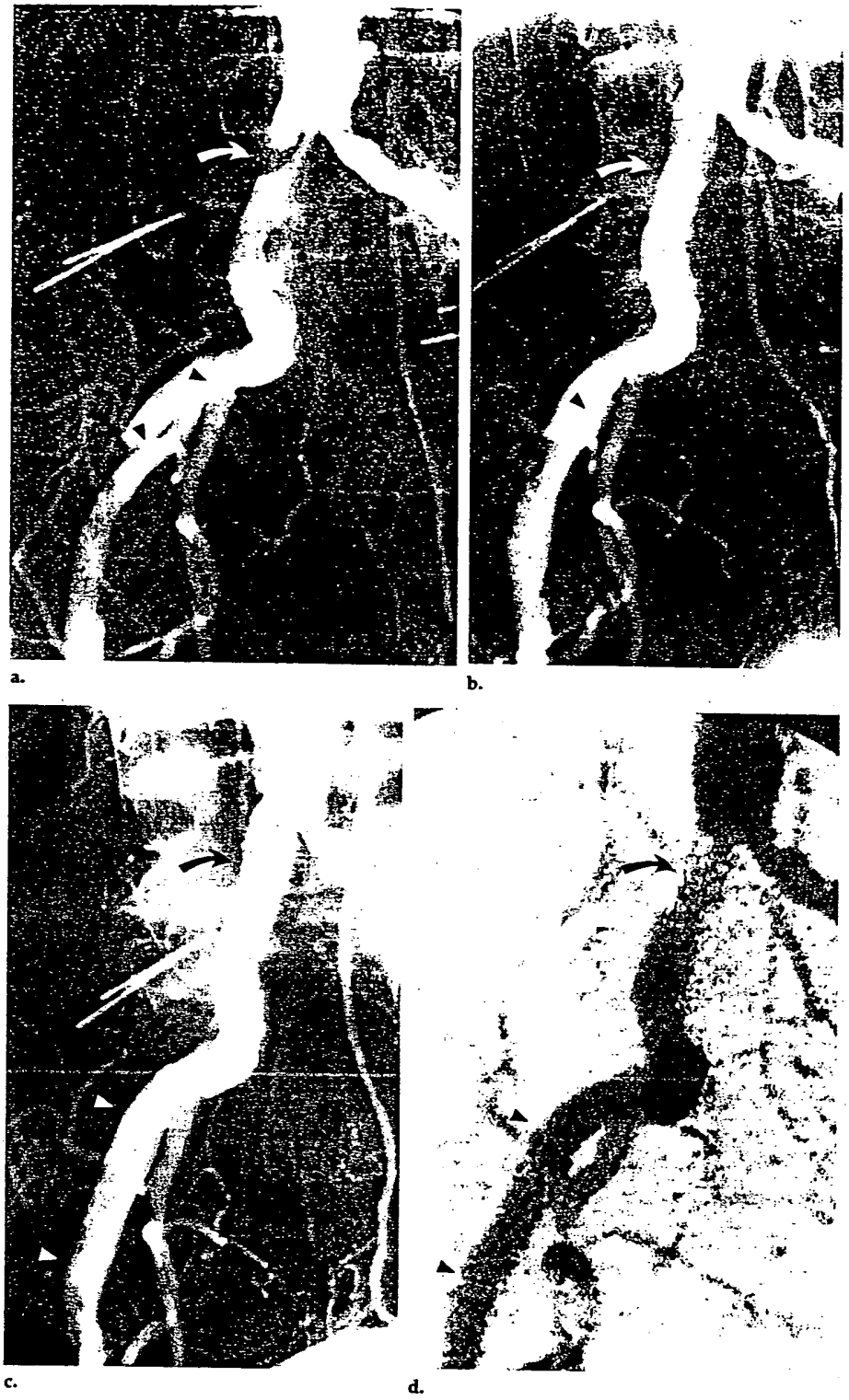

Figure 4. Arteriograms of 69-year-old man with rest pain in the right calf and gangrene of the first toe of the right foot. (a) The right proximal external iliac artery has an area of dissection (arrowheads) after attempted coronary arteriography. An ulcerated atherosclerotic stenosis is seen in the proximal right common iliac artery (arrow). (b) After balloon angioplasty of both lesions, persistent dissection is seen in the proximal external iliac artery (arrowhead). A residual mean gradient of 32 mm Hg was present. The common iliac artery shows adequate dilation (arrow). (c) A single stent was placed in the area of dissection immediately below the ostium of the internal iliac artery (arrowheads). The common iliac artery remains patent. (d) Intravenous digital subtraction arteriogram obtained 6 months after c. The stent area remains patent (arrowheads). The right common iliac artery shows evidence of recurrent stenosis (arrow).

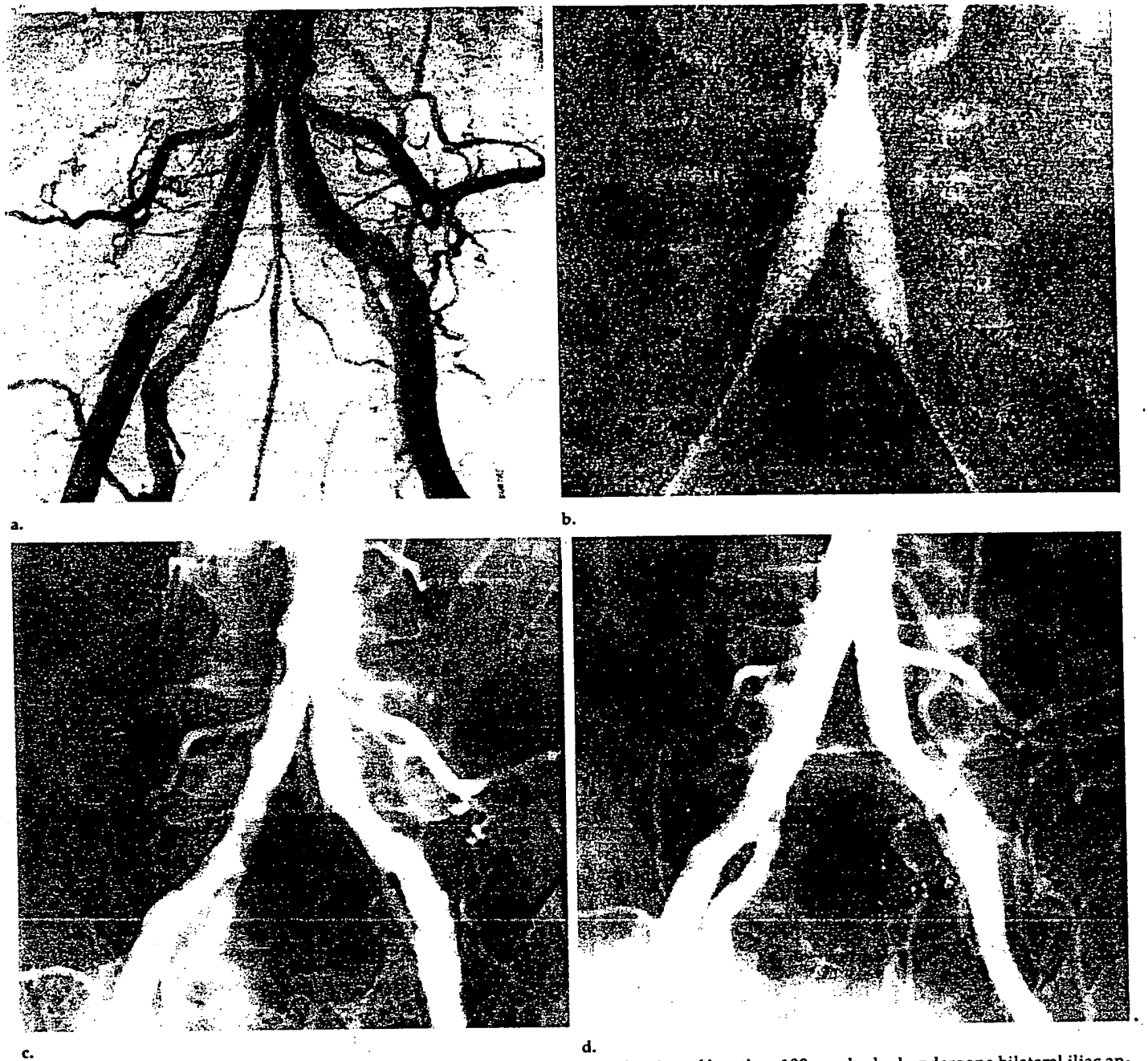

Figure 5. Arteriograms of 63-year-old man with bilateral intermittent claudication of less than 100 m who had undergone bilateral iliac angioplasty 12 months prior to this study. **(a)** Recurrent stenosis at the origin of both common iliac arteries is seen. Postvasodilation gradients of 11 mm Hg in the left and 18 mm Hg in the right artery were measured. **(b)** "Kissing balloon" angioplasty was done with two 8-mm balloons. **(c)** Postangioplasty aortogram shows residual stenosis at the origin of the left iliac artery and dissection of the left lateral aspect of the distal aorta. **(d)** Two stents in tandem were placed in the right common iliac artery and one in the proximal left common iliac artery. The cranial end of the proximal stents make contact in the midline to expand the most distal part of the abdominal aortic lumen. No aortoiliac pressure gradient was present after stent placement.

such a goal may be only partially met by percutaneous angioplasty alone, since as many as 24% of patients undergoing this procedure are left with pressure gradients equal to or greater than 10 mm Hg at rest (5,6,11). The notion that improved flow provided by stents produced superior hemodynamic benefit in this series is supported by the very low posttreatment average gradient of 1.6 mm Hg ± 2.7 (mean ± SD). Only 2.9% of the iliac arteries with stents had a postprocedure gradient of 10 mm Hg or more. This improved inflow was an obvious benefit to distal revascularization surgical procedures. Twenty-five percent of the patients with limbs at risk underwent a combination of iliac artery stent placement and surgery under local or epidural anesthesia. The increase in the ankle-arm index at the latest follow-up examination was greater among patients in this category than in patients with a lesser degree of involvement (Table). The combined approach in patients with threatened limbs yielded a greater hemodynamic improvement than it did in patients with claudication.

While randomization of therapy is the most accurate means of evaluating a new procedure, this approach was precluded by our protocol design, since only failures of angioplasty were subject to stent placement. In general, patients with advanced, complex lesions received stents; those with limited, focal dis-

ease were treated successfully with balloon dilation. This imposed a bias in favor of patients treated with angioplasty that made them unsuitable for comparison. Patients with stents had more advanced disease, as indicated by their 28.9% frequency of limbs at risk for amputation. This stands in contrast to an average 16% of patients in iliac angioplasty series in this category (5,7,12,13).

Eighty-nine percent of the patients receiving stents showed clinical benefit at the latest follow-up examination. This correlates well with the decrease in intraluminal pressure gradient measured at the time of the procedure and the maintenance of increased Doppler pressure indexes at follow-up. The absence of initial benefit or the loss of transient benefit in the remaining patients was marked either by the presence of untreated distal disease or the interval development of new disease that caused limiting symptoms in the opposite lower extremity. Survival statistical analysis of the influence of risk factors, runoff, and the nature of the lesion on long-term benefit will be evaluated when sufficient data become available.

Study of the single autopsy specimen obtained suggested that stents are incorporated in the arterial wall through a process of intimal tissue embedding and endothelialization. This was consistently observed in laboratory animal experiments within 1–3 weeks after stent placement (14–16). However, the presence of residual thrombus in the autopsy specimen, 2 months after stent placement, suggests that these devices may heal in humans at a slower rate than in rabbits, pigs, or dogs.

Complications directly related to the stent added to those related to the procedure amounted to 11.7%. This compares with the average 9% complication rate of reported iliac angioplasty series (3,7,17,18). Particular attention should be directed toward the episodes of acute thrombosis, since this procedure involves the permanent implantation of prosthetic material. It has been shown in animal experiments that low flow predisposes to stent thrombosis (19). The acute occlusion that occurred in the patient in whom a stent was placed proximal to a stenosis is easily explained and, therefore, preventable. The multiple occlusions that occurred in the patient with systemic lupus erythematosus receiving corticosteroid therapy are more difficult to understand. Stent placement should be avoided, or performed with adequate long-term anticoagulation, in patients suspected of having hypercoagulability.

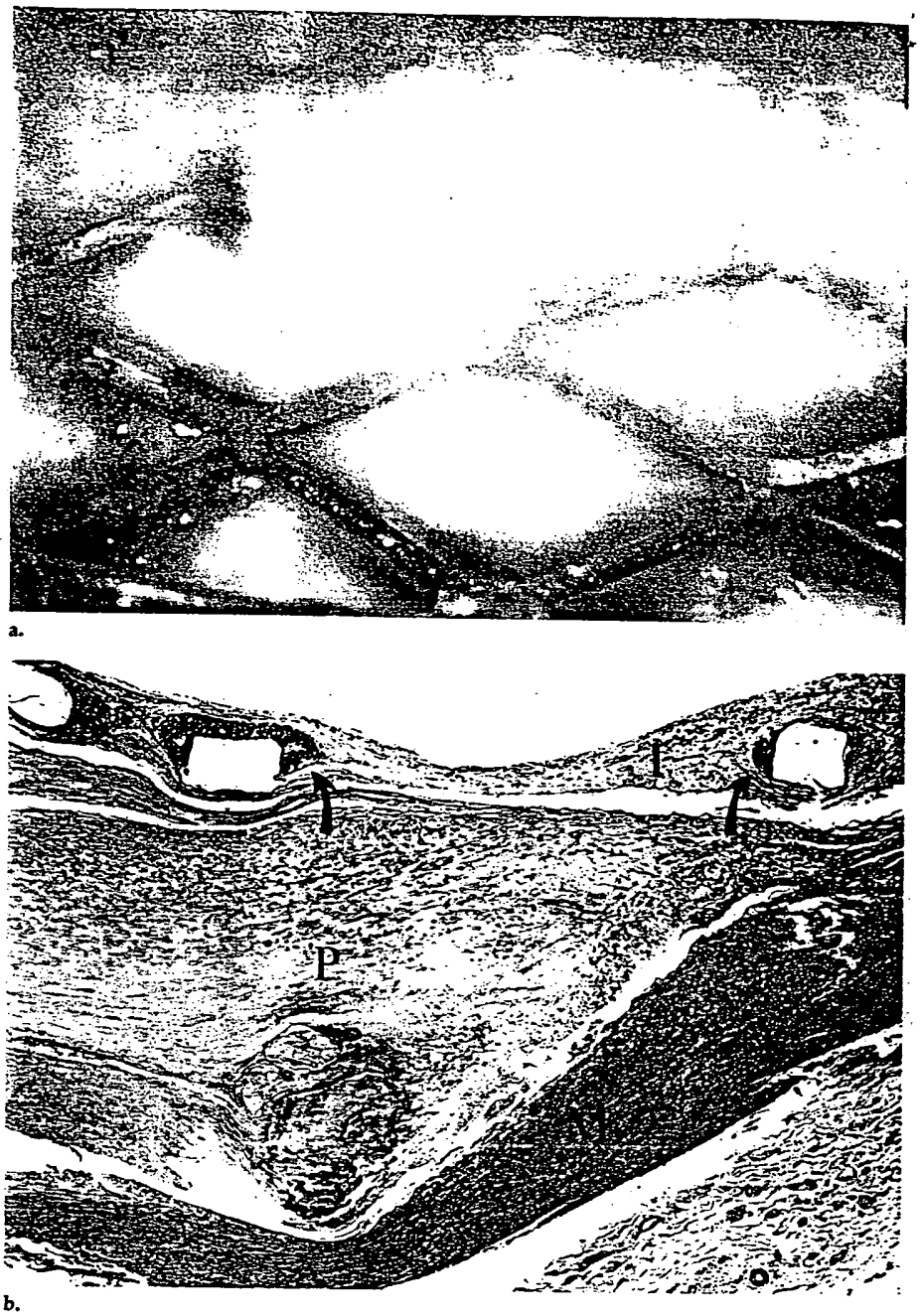

Figure 6. Gross specimen of right common iliac artery with stent in a 68-year-old patient who died of metastatic carcinoma of the lung 2 months after stent placement for stage IV peripheral vascular disease. The stent is covered with a thin, translucent tissue layer. The dark areas adjacent to the stent struts in the lower part of the figure represent residual thrombus (original magnification, ×18). (b) Cross section of the artery. The rectangular spaces near the luminal surface (top) correspond to removed stent struts. Residual thrombus surrounds the strut spaces (arrows). Intimal tissue (*I*) covers the stent and the partially calcified plaque (*P*), which appears displaced eccentrically, compressing the surrounding media (*M*) (hematoxylin-eosin; original magnification, ×54).

Extravasation at the target site as a result of balloon dilation, laser angioplasty, or any other type of instrumentation is an absolute contraindication to stent placement because a stent would intensify bleeding by enlarging the defect in the wall.

The limb amputation that occurred after stent placement in one patient was not considered a complication of the treatment because the stent was placed to forestall impending limb loss from severe diabetic vasculopathy. After below-the-knee amputation, the improved ipsilateral femoral pulse and thigh pressures suggested

that the level of amputation might have been higher without the enhanced inflow afforded by the stent.

The peripheral embolization of organized nonlysable material in the three patients with chronic iliac occlusions suggests caution in using preliminary dilation and percutaneous stent placement when the iliac artery obstruction is extensive (ie, >6 cm). Subsequently, we treated lengthy iliac occlusions without complication by exposing the access site surgically and attaining distal control of the ipsilateral femoral vessels to avoid embolization.

In conclusion, the relatively early results from this trial indicate that stent placement may be a safe and effective means of treating atherosclerotic iliac artery disease that does not respond favorably to balloon angioplasty. ■

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BY LORI D'AGINCOURT

Stents aid PTA in battle to reduce restenosis rates

The stents now available are just the first generation of their kind. Further miniaturization of stents and their introductory catheters is expected, as is greater variety of shapes and sizes. Researchers are also working on biodegradeable stents, coating stents with antithrombogenic materials, and exploring the possibility of combining stents with drug delivery.

Despite progress made by a host of new intravascular devices, the long-term success rate of percutaneous transluminal angioplasty remains low. Restenosis averages 25% to 75%, depending on the vessel treated. Stents may soon star in the battle against abrupt closure and restenosis, however, by acting as a mechanical brace when angioplasty fails.

Most experience has been gained in the coronary arteries, but the peripheral vessels represent the next frontier for intravascular stenting. Stents have been placed in the iliac, renal and femoropopliteal arteries with varying degrees of success. They have been used to open up large veins, as well as the mesenteric artery, celiac trunk, clavian and carotid arteries. They are allowing radiologists to manage patients with portal hypertension and recurrent variceal bleeds, a group previously not treatable.

There are few limitations to potential uses for intravascular stents. Theoretical applications include closure of saccular and fusiform aneurysms and arteriovenous fistulas. Coated stents can easily be tailored to act as flow restrictors or even occluders of large vessels.

While stents may not prevent restenosis, they have proved extremely valuable in treating complications of angioplasty. Although infrequent, dissection has demanded immediate surgery until now. Stents can hold back the dissected flap, converting traditional failures into success.

"For the appropriate indication, such as dissection or recoil of the iliac

FIGURE 1. By tackling iliac artery occlusions, intravascular stents open up new group of patients to percutaneous therapy. A: Occlusion of common iliac artery before stent. B: Catheter carrying Strecker stent moves into position. C: Artery after stent implantation. (Provided by E. Strecker)

artery, stents are going to make a tremendous difference in the outcome of angioplasty. They will be a real help to the average interventionalist," said Dr. Arina van Breda, director of interventional radiology at Alexandria Hospital in Alexandria, VA.

Researchers agree it is unlikely that stents will offer a stand-alone alternative to PTA, however. Iliac artery trials have been under way for almost four years now, and at 36-month follow-up, about 34% of these patients have had recurrent symptoms. Paralleling experience with PTA, outcomes are not as good in small-diameter vessels such as the femoral or renal arteries. Coronary stenting has also been plagued by fibrointimal hyperplasia and thrombosis.

Yet while intravascular stents may not have kept up with their initial fanfare, investigators are quick to emphasize that these devices are very new. Indications for their use are still being defined and appropriate anticoagulation regimens remain to be worked out. Further, stents may prolong patency in certain vessels by acting as a mechanical buttress, but they do not directly attack the problem of restenosis.

"Stents are not the answer to restenosis," said Dr. Mark H. Wholey, chairman of diagnostic imaging at Shadyside Hospital in Pittsburgh. "We have to control the intima first. This may involve some drug delivery system or biologic control of the endothelium combined with mechanical devices."

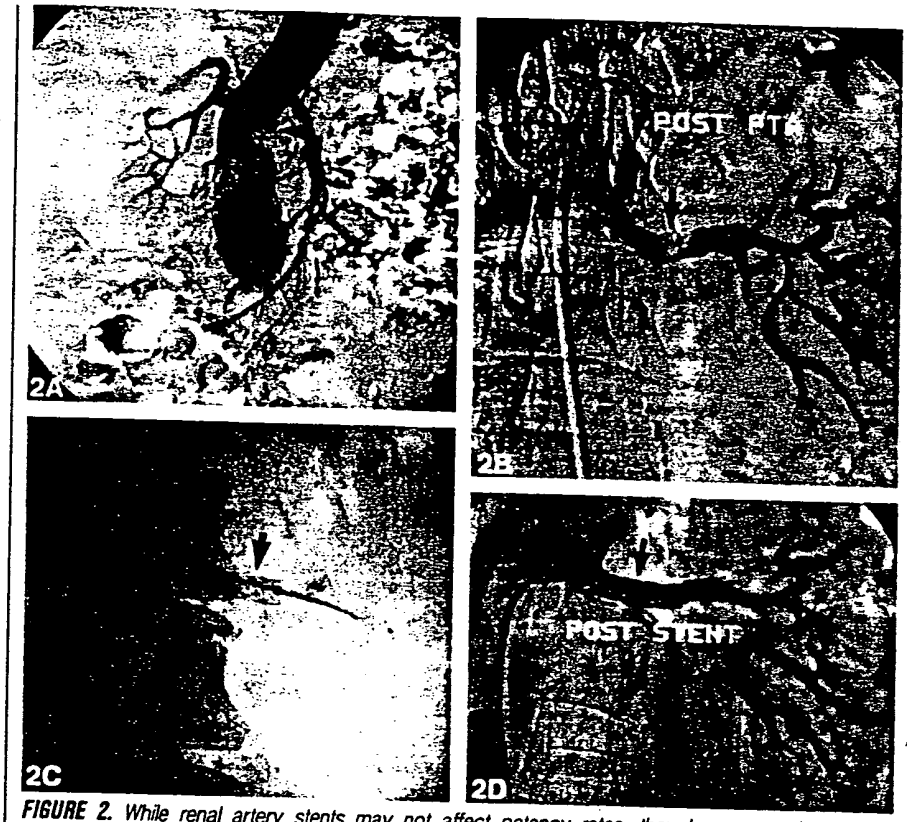


FIGURE 2. While renal artery stents may not affect patency rates, they have proved extremely valuable in problem situations. A: Occluded left renal artery. B: Residual stenosis can be seen after recanalization and angioplasty. C: Stent placement. D: Artery is widely patent after stent placement. (Provided by A. van Breda)

Researchers also acknowledge that availabie stents represent just the first generation of devices. Stents and their introductory catheters are expected to be miniaturized further. There will also be a greater variety of shapes and sizes from which to choose, many tailored for specific situations. Researchers are also working on biodegradable stents, coating stents with antithrombogenic materials and exploring the possibility of combining stents with drug delivery.

Indeed, the development of new therapy involving prosthetic material puts the interventionalist into competition with surgeons' 40 years of experience with surgical vascular implants, said Dr. Julio C. Palmaz. The technology is evolving rapidly and what the future holds is uncertain.

"We must follow a methodology similar to that used in research of surgical grafts. This includes studies on biomechanics, biocompatibility and thrombogenicity," said Palmaz, chief of cardiovascular and special intervention at the University of Texas, San Antonio.

ILIAC STENTS

While many stents are under investigation, four types have dominated the clinical scene: the Palmaz, Strecker and Gianturco stents, and the Schneider or Wallstent. The Palmaz

While intravascular stents have fallen short of initial hopes, they have a role to play in acute closures post-angioplasty

and Strecker stents are balloon-expandable, while the Gianturco and Schneider stents are self-expanding. Further, the Palmaz and Gianturco stents are relatively rigid, in contrast to the Strecker and Schneider stents, which retain some longitudinal flexibility.

The first FDA-approved vascular stent application will be in the iliac arteries. Although most iliac lesions respond well to PTA, stent placement may offer a solution in difficult cases, such as eccentric stenoses and occlusions. The external iliac artery, which is a notoriously poor responder to angioplasty, may also be a prime place for stenting.

To date, most experience has been acquired with the Palmaz stent. Iliac artery trials have been under way for four years at 13 sites, with over 375 patients receiving stents. At 36-month follow-up, the success rate is 66%, Palmaz said. Complications average 12.9%, with most problems (10%) arising from the management of the puncture site, he said.

Based on these results, Palmaz now places iliac stents when there is 30% reduction of lumen size after PTA, and/or a mean pressure gradient of 5 mmHg or more. Thus the main indication for their use is for treating complete occlusions, failures of previous PTAs, dissection or elastic recoil, and patients with ulcerated lesions at risk of embolizing with PTA.

Dr. Geoffrey Gardiner, who participated in the multicenter trial, is also encouraged by results with the Palmaz stent. Gardiner and coworkers from Thomas Jefferson University in Philadelphia placed stents in stenotic iliac arteries of 20 patients. When compared to PTA, stenting provided a consistently better outcome, he reported at the 1990 meeting of the Radiological Society of North America. Average residual stenosis was 2% after Palmaz stent placement versus 39% with conventional PTA.

While the team awaits long-term findings before making conclusions about the role of stenting in iliac disease, Gardiner noted that the early angiographic findings are impressive.

"When one looks at the initial results, how wide the lumen is, how smooth the vessel, there is a significant improvement with the stent compared to just the balloon," said Gardiner, director of interventional radiology at Thomas Jefferson University.

Findings obtained with the Schneider stent have been equally auspicious. Dr. Rolf W. Gunther and colleagues from the Technical University of Aachen, Germany, placed stents in 55 patients with iliac occlusions. The group was able to restore

BY MARK WHOLEY, M.D., AND MICHAEL LIM, M.D.

LONG-TERM PATENCY REMAINS PROBLEMATIC

Design advances spur progress in stent uses

In 1964, the visionary cardiovascular radiologist Charles Dotter proposed that stainless steel stents or nitinol coils in either an intravascular or paravascular position would someday be an option for patients with totally occluded vessels. His concept became a reality almost 25 years later, when Swiss cardiologist Ulrich Sigwart successfully implanted a coronary artery stent.

Intravascular stents are among the new technologies that have transformed PTCA and PTA from a procedure limited to low-risk patients to one that is being offered to patients with complex peripheral, coronary and even vertebrobasilar and carotid occlusive disease. In addition to stents, a series of laser systems, high- and low-speed rotational devices, and both forward- and side-cutting atherectomy devices have been introduced for both the peripheral and coronary circulation. Yet the restenosis rates have not changed dramatically since Gruentzig's first angioplasty in 1977.

Restenosis, acute occlusions, and excessive dissection at the angioplasty site continue to plague the interventionalist despite adjunctive systemic measures such as anticoagulation and intensive antiplatelet therapy. With a restenosis rate of 25% to 40% in the coronary circulation and even higher restenosis rates in totally occluded superficial femoral vessels, it was hoped that the new interventional devices would offer some improvement. Certainly stents have been promising as bail-out devices in acute occlusions, but are not by themselves the answer to restenosis.

The satisfactory results with iliac stents cannot easily be translated to the smaller coronary vessels. It has been fairly well established that iliac stenosis, and even iliac occlusions, do fairly well with simple balloon angioplasty. The recent report by Serruys of 32% restenosis in 117 self-expandable wallstents exemplifies the problem of stents. Schatz's report on 299 balloon-expandable Palmaz-Schatz stents demonstrated a significant decrease in the incidence of subacute closure from 18% to 0.6% when aggressive anticoagulation was initiated, but the study did not address the problem of late restenosis.

Schatz's aggressive anticoagulation regime included aspirin, dipyridamole, low-molecular-weight dextran, heparin and warfarin. All of these, along with the inherent characteristics of the Palmaz-Schatz stent,

***DR. WHOLEY** is chairman of diagnostic imaging and **DR. LIM** is a fellow in radiology at Shadyside Hospital in Pittsburgh.*

flow in all patients, although two reoccluded at two months. Restenosis had occurred in only two additional patients at 13-month follow-up.

Other researchers are successfully treating iliac lesions with the Strecker stent. Made of a knitted tantalum mesh, it demonstrates excellent radiopacity and flexibility. Tantalum, which is used for making surgical clips and orthopedic implants, has proven biocompatability, said Dr. Ernst-Peter Strecker, a professor of radiology at the University of Freiburg in Germany.

Strecker and his colleagues have inserted iliac artery stents in about 55 patients. The patients presented with different symptoms: necrosis, rest pain and severe claudication. With the longest observation being 48 months, the group has observed no reocclusions and only one restenosis.

By tackling iliac artery occlusions, intravascular stents open up a whole new group of patients to percutaneous techniques, Strecker said (Figure 1). Traditionally, iliac artery occlusions responded poorly to balloon angioplasty. It was possible to treat the occlusion with fibrinolysis and then dilate the vessel, but this was very time-consuming.

"If you dilate an iliac artery occlusion with PTA, it usually collapses afterward. But now we can implant the stent and completely open the lumen. It is a very elegant method, something we couldn't do before," Strecker said.

He noted that a prerequisite to successful stenting with the Strecker device, however, is normal expansion of the balloon. It is sometimes impossible to open the balloon completely in very atherosclerosed vessels. If the balloon does not assume its normal shape first, the stent may not expand fully, he said. This is different from self-expanding stents, which gradually widen themselves.

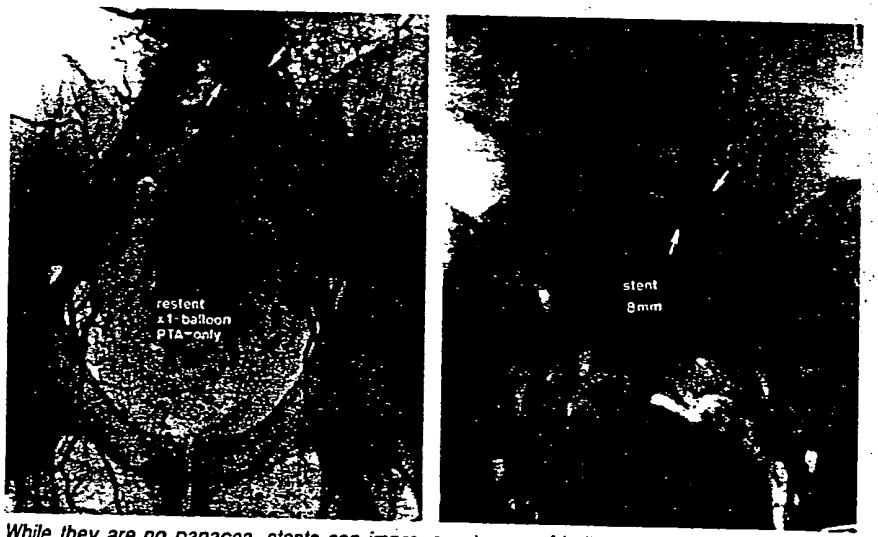
STENTS REPLACE PTA?

While most studies have focused on problem patients, one group is exploring the efficacy of using intravascular stents as primary treatment for iliac artery lesions. Drs. Goetz M. Richter, Thomas K. Roeren and investigators from the University of Heidelberg in Germany began a randomized trial in 1987 to test stenting versus regular PTA in the iliac arteries.

Presently, 166 patients are enrolled in the trial (82 stents; 84 PTA), said Roeren, an assistant professor of radiology. At a mean observation time of 18 months, initial results indicate that stenting of primary iliac occlusive disease may achieve a higher level of clinical success. Patency rates are slightly higher in the stented

were responsible for resolving many of the problems related to acute and subacute closure. The stents provided a lattice structure upon which orderly thrombosis can occur without disruption of the laminar flow. The mechanical support provided by the stent resists the effects of elastic recoil and vasospasms and tacks up the intimal flaps, thereby reducing the likelihood of early stent closure.

Stents have not, however, overcome the problem of intimal hyperplasia and progression of atherosclerosis, which are important mechanisms for the late restenosis. Furthermore, in certain of the articulated segments, restenosis occurs at that articulated stent component. In itself, expansion of the stent could result in vascular injury stimulating the release of platelet-derived growth factors, and alteration of smooth muscle cell function. The ability to modify the biological response and the variability of smooth muscle cell proliferation, platelet deposition, and the endothelial release factors are still poorly understood.



While they are no panacea, stents can improve outcome of balloon angioplasty in appropriate patients. Left: Stenosis with essentially total occlusion is visible near origin of left common iliac artery. Right: 8-mm Palmaz-Schatz stent in satisfactory position shows marked improvement in overall dimensions and flow. (Provided by M. Wholey)

At least seven intravascular stents are under active clinical or investigational trials. The delivery systems, the expansion ratios, the overall expandability, and the radiopacification are features that will be continually improved. New indications will also occur as the stents are used as a nonsurgical alternative for abdominal aortic aneurysmal and occlusive disease. But it may be that the destiny of stents lies not only in design advances but also in research into biological response modifiers to ensure long-term patency. ■

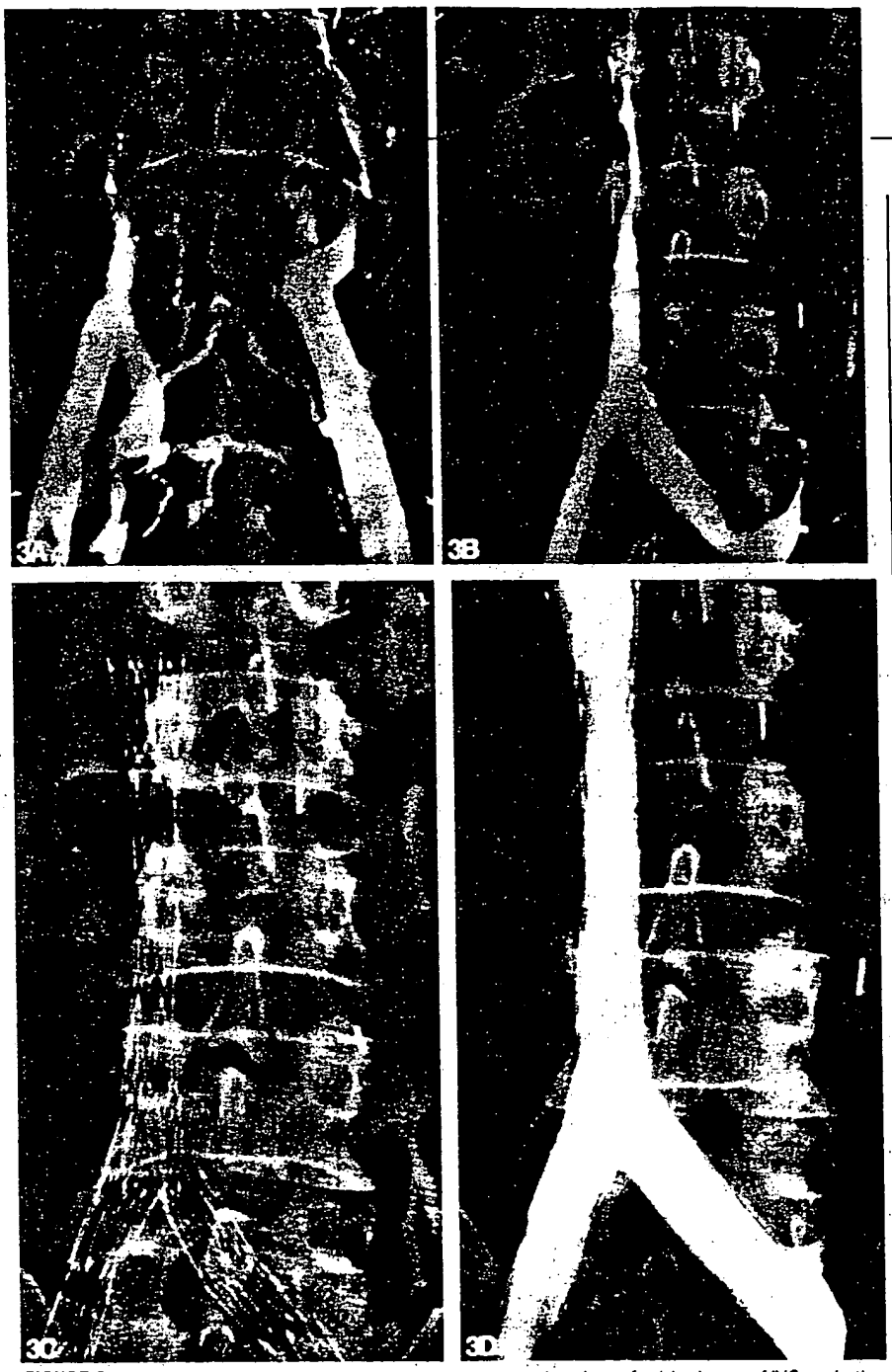


FIGURE 3. *Using Gianturco stent, investigators have stented patients for blockage of IVC and other large veins. Images shown here are of 55-year-old man with severe leg and scrotal edema.* ***A:*** *Control study.* ***B:*** *After urokinase infusion.* ***C:*** *Immediately after stent placement.* ***D:*** *Five months after placement. Patient showed no recurrence of edema 11 months after stenting. (Provided by J. Rösch)*

group than those receiving PTA.

While five-year survival data are needed to establish any real advantages of primary stenting over PTA, the initial results do not come as a surprise, Roeren said. In one sense, stents are designed to treat their own complications, he said.

"One of the few setbacks with balloon angioplasty in the iliac arteries is dissection. If I have a dissection while placing the stent, the stent will tack the dissection to the wall. In contrast, when I deflate the balloon after angioplasty, the dissection hangs free into the artery and may lead to occlusion," he said.

Another advantage of the stent is that it has been designed primarily to prevent recoil of the artery, which the balloon cannot do, Roeren said. On the other hand, a stent may ultimately act as a thrombogenic foreign body within the artery, although this does not seem to have clinical import in wide-diameter vessels like the iliac artery.

Despite the success of intravascular stents in the iliac arteries, there is a learning curve to the technique, Palmaz cautioned. Results from the trial with his namesake stent showed that complications were fewer in centers that placed more than 10 stents. In contrast, institutes that inserted fewer than 10 stents had more complications than the average rate for the whole trial.

Hematoma was the most common complication, due primarily to the large (10-French) introducer system, Palmaz said. Stent-related complications included occlusion due to thrombosis in a few cases, although these patients had hypercoagulability syndrome. Three pseudoaneurysms were also reported. All occurred in patients who had first undergone revascularization with a hot-tip laser for complete occlusion.

Based on this finding, Palmaz advised caution in stenting patients who have received procedures that may perforate the vessel wall. Stenting carries a high risk of intensifying bleeding by opening up the perforation, he said. It is thus mandatory to rule out perforation before considering stent placement.

"In patients who have received laser revascularization, I advise exhaustive measures to rule perforation out. For example, I am leery about doing laser revascularization in the OR environment where the x-ray equipment is poor. You need superb x-ray documentation after laser angioplasty to rule out perforation," Palmaz said.

RENAL ARTERIES

While stents have performed extremely well in the iliacs, their role in the renal arteries remains open to question. Initial hopes that stents would improve patency rates for treating renal osteal lesions have not been borne out. Small vessel size and complex renal lesions create problems for stenting, similar to those exper-

ienced in angioplasty.

Renal artery stenting has also created a new set of demands. Because of the need for greater flexibility in the renal arteries, Palmaz developed a two-segment (8-mm diameter) stent. The advantage of the segmented stent is that it can cross curves, which is often mandatory for placement in the renals, Palmaz said. Of about 50 patients who have received this stent so far, average luminal diameter at six-month follow-up is 37.2%, he said. Immediately before angioplasty and stenting, patients averaged an 86% reduction in lumen size. About 16% of stents restenosed.

Investigators using both the Wallstent and the Strecker stent have also had mixed results in the renal arteries, reporting restenosis rates from zero to 30%. Variability has occurred not only among different types of stents, but among different centers using the same stent. Experience is limited, but stent restenosis appears to be a recurring problem.

Intimal hyperplasia is likely the main culprit for restenosis, but much needs to be learned about renal artery stenting, Palmaz said. For example, his group is just beginning to establish appropriate anticoagulation regimens. His initial series was performed without anticoagulation, which probably contributed to the relatively poor results. Patients are doing much better following renal artery stenting now that they are given anticoagulation therapy, he said.

Palmaz stressed that results are also influenced by the fact that renal artery stenting is being evaluated in patients with the worst disease.

"In the last six patients we stented, two had renal failure, four had diabetes, and all had evidence of coronary or peripheral vascular disease. So we are evaluating a method in patients who are already failures of other methods and have very advanced disease. Taking that perspective into account, I think the results are encouraging enough to continue the trial," he said.

While renal artery stents may not affect patency rates, they have proved

FIGURE 4. *Transhepatic portosystemic stent shunting is making progress towards managing patients with recurrent variceal bleeding and advanced liver cirrhosis. Study shows portal vein (PV), hepatic vein (HV) and shunt with stents (arrows). (Provided by A. van Breda)*

extremely valuable in problem situations. Van Breda said that as a "bail-out" device, stents have allowed her to save a PTA in a number of cases (Figures 2 and 5). She described a patient who suffered immediate reclosure following angioplasty for a renal artery occlusion. Without the stent, the case would have been considered a failure.

"We were able to recross the reocclusion, which was due to a large intimal dissection, and then place the stent. We achieved a beautiful anatomic result and more impressively, a great clinical result: the hypertension completely went away. That is the infrequent, but dreaded complication of angioplasty, for which renal stents are going to be a tremendous help," van Breda said.

Dr. Chet R. Rees also believes that stents may serve as an effective option in failures of angioplasty. Much may change, however, as researchers gain more experience with stents, he said. For example, little is known about the relative advantages and disadvantages of spring-type versus balloon-expandable stents in the arteries. Coating the stents with antithrombotic agents may also have a big impact on how the artery reacts to the stent, he said.

"As we learn more, we are going to have a better handle on who should be stented and who should not be. It is a rapidly evolving field. There is no bottom line at this stage," said Rees, a radiologist at Baylor University in Dallas.

FEMOROPOPLITEAL VESSELS

Although it is early for predictions, the femoropopliteal vessels may represent the next frontier for intravascular stenting. The total occlusion and reocclusion rate is so high in the superficial femoral that it offers an ideal target for stenting. But similar to the renal arteries, restenosis is expected to be a major problem, because of the small size and slow flow within these vessels.

Indeed, Strecker and his colleagues have implanted more than 60 stents into the femoral arteries. According to his results, with a maximum follow-up of 30 months, restenoses ranged from 10% to 30%, depending on location of the lesion. There was more restenosis or reocclusion in the distal femoral artery, for example, than in the proximals. Stents implanted into the common femoral artery and the proximal portion of the superficial femoral artery had better long-term patency, he said.

Using the Schneider stent, Gunther and his colleagues from the Technical University of Aachen have encountered a restenosis rate in the femorals near 40%. Despite the low patency rate, however, these lesions responded well to further intervention, he said.

"We saw some patients in whom restenosis occurred due to intima hyperplasia and we treated them with the Simpson atherectomy catheter. There was no restenosis after removal of the hyperplastic intima," he said.

Success in the femoral arteries may also be affected by medical therapy, Strecker said. He has compiled results from another group of 20 patients who received coumadin following femoral stenting instead of platelet aggregation inhibitors. This group displayed a

FIGURE 5. *Flexibility of some stents allows their use in eccentric calcified stenoses.* ***A:*** *Iliac artery stenosis before treatment.* ***B:*** *Residual stenosis after angioplasty.* ***C:*** *Stent after deployment.* ***D:*** *Artery appears widely patent after stent placement. (Provided by A. van Breda)*

better prognosis, with only 10% restenosis or reocclusion following stent placement, Strecker said.

ANCILLARY APPLICATIONS

While stents will ultimately gain their greatest use in arterial disease, venous disease is emerging as a secondary application. Indeed, Dr. Josef Rösch and colleagues at the Oregon Health Sciences University in Portland have used stents to treat venous obstructions with success. Rösch is a professor of radiology.

Using a modified version of the Gianturco stent, Rösch has stented some 33 patients for blockage of the inferior and superior vena cava and other large veins (Figure 3). In patients with SVC syndrome, stent placement resulted in normalizing SVC circulation, he said. The cyanotic and plethoric facial complexions of the patients returned to normal immediately after stenting, and their headaches disappeared shortly thereafter. Edema regressed from the face and neck in one day, and from the extremities and upper trunk in two to three days.

At the M.D. Anderson Cancer Center in Houston, Dr. Chusilp Charnsangavej and coworkers have achieved a 75% success rate in relieving symptoms of patients with malignant compression of the SVC or IVC. A complication that occurs in 20% to 30% of patients, however, is stent jumping, he said. Instead of staying in the stenotic site, the Gianturco stent may spring out into the area of normal vessels following its release. Multiple stent placement may help overcome this problem by preventing slippage, Charnsangavej said.

Wholey and his colleagues have also used the Palmaz iliac stent in managing vena cava syndromes caused by malignancy. These patients often have marked facial and upper extremity edema, and have no treatment option other than radiation or chemotherapy. Although results are short-term, the SVC stents produced dramatic improvements, Wholey said.

"Even for palliative relief of cerebral edema, the SVC stents have been tremendous. In those cases, we have used the 8-mm Palmaz stents and taken them as high as 15-16 mm with valvuloplasty balloons," he said.

Although patient numbers are limited, Rösch has also placed stents in the hepatic veins and IVC of those who had Budd-Chiari syndrome. The stents offered palliative relief of obstructions in patients who would otherwise be difficult to treat, he said.

Another group that may reap the benefits of stenting are patients with hemodialysis shunts. Initial studies indicate that stents may improve and prolong the life of hemodialysis shunts, although they ultimately are prone to intimal hyperplasia. Repeated intervention, usually PTA or atherectomy, is eventually required to maintain patency of the stented shunt.

"We have had quite a few patients who had a malfunctioning or failing shunt and there was no means of treatment other than stent placement," Gunther said. "But restenosis by hyperplasia, although it can be easily managed by percutaneous means, should limit its use to desperate cases."

PORTOSYSTEMIC SHUNTS

In addition to improving the results of PTA, stents are allowing radiologists to test their skills in totally new areas. One of the most exciting percutaneous techniques developed in recent years is transhepatic portosystemic stent shunting (TIPSS).

TIPSS is making progress towards managing patients with recurrent variceal bleeding and advanced liver cirrhosis, a group that until now has not been treatable, van Breda said. Liver transplantation might be considered in these patients, but they are often too sick to undergo surgery. Their alternatives are ghastly—usually death by variceal bleeding.

"Having this procedure will allow us to offer at least some stabilization management until more definitive treatment becomes available. It is a tough group of patients to treat for a lot of reasons," she said.

The technique involves entering the liver from a transjugular route. An intrahepatic hepatic-vein to portal-vein tract is created using a 5-French transjugular needle sheath. The connection is maintained by the stent (Figure 4).

FIGURE 6. Endoluminal polymer paving catheter. Polymer is in place over combined dilating and heating balloon. (Provided by M. Slepian)

Drs. Roy Gordon, Ernest Ring and Jeanne LaBerge from the University of California at San Francisco have performed over 20 TIPPSS procedures using the Wallstent. The results have been encouraging, with patients demonstrating excellent diversion of blood flow across the portosystemic shunt. The procedure appears to be effective in preventing recurrent gastrointestinal hemorrhage from bleeding varices.

"The real attraction of this procedure is that it obviates the need for a huge surgical operation. It gets the patient into good condition for liver transplantation without affecting the operative field," said Gordon, a professor of radiology at UCSF.

Other groups have also had success performing the procedure with the Palmaz stent. Dr. Goetz Richter, an associate professor of radiology at the University of Heidelberg, reported his findings in 19 patients at the 1991 meeting of the Society of Cardiovascular and Interventional Radiology. After one year, his group observed a 70% survival rate, and all patients had well-functioning shunts.

Investigators are also exploring the feasibility of using stents for performing percutaneous bypass of abdominal aortic aneurysms. Using dogs as an experimental model, Palmaz created a transluminal bypass by suturing a stent to the partially overlapping end of a tubular graft. In this way, stent expansion pressed the graft against the aortic wall, creating a watertight seal. The stent-graft assembly was mounted on a balloon angioplasty catheter, and introduced through a 14-French sheath through a femoral arteriotomy.

His animal experiments demonstrated exclusion of the aneurysm and flow through the graft at six-month follow-up, Palmaz said. The procedure has now been performed in four patients in Europe. Although the patients are doing well at this time, he stressed it is too early to say whether the procedure is safe or effective.

THE HEART

The greatest experience with intravascular stents to date has been in the heart. Enthusiasm has been dampened by reocclusion and high restenosis rates, however. Thus, while stents may play a role in select patients, it is unlikely they will be used routinely in their present form.

In the January issue of the *New England Journal of Medicine*, Dr. Ulrich Sigwart and colleagues from six European centers reported their results in the first 105 patients who received the Wallstent. Although there was an immediate increase in luminal diameter following implantation, occlusion occurred in 24% of patients within the first 14 days. The restenosis rate climbed as high as 14% when the criterion of 50% stenosis was used. Three patients died because of acute closure one to eight days after implantation. Another three patients died suddenly, suggesting that their stents also became blocked.

Although intravascular stents have fallen short of initial hopes, they have a role to play in acute closures following angioplasty and in treating dissections, said Sigwart, director of invasive cardiology at the Royal Brompton National Heart and Lung Hospital in London. He also recommended their routine use in diseased coronary bypass grafts to prevent embolization.

Early thrombogenic occlusion remains a serious problem despite anticoagulation, however, Sigwart said. Investigators have begun to tackle this obstacle by coating stents with antithrombogenic materials. Other research endeavors have focused on biodegradable stents or combining stents with drug delivery.

Dr. Marvin Slepian, director of interventional cardiology at the VA Medical Center in Tuscon, AZ, has developed a process called endoluminal paving and sealing. The goal is to resurface the endoluminal surface of a vessel with a thin film of biodegradable polymer, he said. A polymer tube is introduced via a catheter (Figure 6), heated and then custom molded with a balloon to the inner surface of the vessel. Within seconds, the polymer is cool and the balloon deflated. The result is a smooth endoluminal surface that may last from six months to two years, depending on the materials used.

In addition to providing vascular support, polymer paving has the potential for delivering drugs directly to the site of injury, Slepian said. The polymer could be impregnated with drugs that would slowly exude into the paved vessel segment. Such agents could include antithrombotics or antiproliferative drugs that may counter thrombosis and intimal hyperplasia that often results from PTA-induced smooth muscle injury.

Investigators from Duke University in Durham, NC, are also working on a biodegradable polymer stent that carries drugs to the atherosclerotic site. The benefit of a stent that absorbs or breaks down over time is that it reduces the chance of long-term complications, said Dr. Richard Stack.

"A restenosis usually declares itself within six months. A bioabsorbable stent can go in after standard angioplasty to keep the vessel open, maintain patency for several months and then disappear," said Stack, director of interventional cardiology.

While the future will bring further refinement in stent design, Sigwart believes that the marriage of these devices to drug delivery holds the key to conquering restenosis.

"Drug delivery is one of the great future applications of stents. It will reduce the amount of anticoagulation the patient takes orally, and modulate the repair mechanism generated by implanting a foreign body," he said. ■

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Percutaneously Placed Endovascular Grafts for Aortic Aneurysms: Feasibility Study[1]

This limited study addressed the feasibility of treating aneurysms with a new transcatheter endoprosthesis. Aortic aneurysms were experimentally created in six dogs and subsequently bridged with nylon-covered, self-expanding metallic stents. The dogs were followed up for as long as 7 months (median, 22 weeks). In each dog, the graft effectively reconstituted the aortic lumen, excluding the aneurysm. One dog exhibited minimal (<1-mm) residual dilatation at the site of the aneurysm 7 months after graft placement. The nylon material acted as a support and template for neointimal encasement, enabling the formation of a new vascular lumen. It also remained porous at the origin of aortic side branches, preserving the visceral blood supply. One of the endovascular grafts failed to expand completely at its distal end, which promoted thrombus formation within the graft and resulted in the occlusion of both renal arteries. The dog was found comatose 48 hours after graft placement and was killed at that time.

Index terms: Aneurysm, aortic, 89.73 • Blood vessels, grafts, 981.1299, 981.458 • Grafts, 981.1299, 981.458

Radiology 1989; 170:1033–1037

In 1969, Dotter inserted stainless steel coils as vascular stents into canine popliteal arteries, which, despite some stenosis, remained patent (1). Innovative new designs and delivery techniques have led to expanded applications in humans (2–9).

There is no satisfactory nonsurgical treatment for aortic aneurysm. A large aneurysm (>5 cm) or an enlarging, leaking aneurysm requires prompt intervention. Regardless of other illness or risk, surgical repair is the only means of averting catastrophic rupture, but it involves significant morbidity and mortality.

In our laboratory, we formulated a nylon-covered, self-expanding metallic endovascular graft that can be introduced by means of a percutaneous transcatheter technique and positioned across an aneurysm. We have previously reported the placement of the graft in the normal canine aorta (10) and report here its use in experimentally created aortic aneurysms in dogs.

MATERIALS AND METHODS

Graft Construction

A self-expanding endovascular graft was constructed and first described by Lawrence et al (11) and later modified by Yoshioka et al (10) to the design used in the present study. The device consisted of three or four small, self-expanding Gianturco stents connected in tandem with two stainless steel struts (0.016-inch wire, 5 cm long) (Fig 1a). Each stent was constructed of 0.016-inch (0.4-mm) stainless steel wire bent into a six-tip zigzag configuration that was 2.5 cm long and had an internal diameter of 15–20 mm. Nylon material (88% nylon and 12% Lycra spandex) was formed into cylinders approximately 7 mm in diameter and either 4.5 or 7.0 cm long. The nylon was secured at each end to the stent framework with a 6-0 monofilament suture. The completed endovascular graft measured 8 cm (three stents) or 11 cm (four stents) in length, with a fully expanded diameter of 11–12 mm. In five of the six grafts, the lead stent was not covered by the nylon material, to afford an anchor (Fig 1b). The sixth graft was fitted with anchoring barbs at both ends (Fig 1c).

Aneurysm Formation

Six adult mongrel dogs were used for this study. Each dog was subjected to general anesthesia with intravenously administered sodium pentobarbital (30 mg/kg) or halothane. After an aseptic left carotid arteriotomy was performed, a 5-F catheter was inserted and advanced under fluoroscopic guidance to a point 1.0 cm above the origin of the right renal artery. Heparin sodium was then administered (100 IU/kg), and baseline angiography was performed (15 mL/sec of Renografin 60 [meglumine diatrizoate; Squibb, New Brunswick, NJ], for a total of 30 mL).

Sterile preparation of the abdomen was performed, and all surgery was done according to sterile technique. A vertical midline incision was made through the peritoneum, and the bowel was gently retracted, exposing the retroperitoneum. Through a combination of sharp and blunt dissection, the loose connective tissue, fat, and adventitia were removed from the ventral surface of the infrarenal aorta, and a 4–6-cm^2 area that had no major side branches was selected. A shallow, vertical midline incision was made in the aortic wall at the selected site, and a thin layer of tunica media was carefully removed from each side of the incision (12). The procedure was continued until 60%–70% of the aortic media had been removed. Ideally, at this point there was definite aneurysmal bulging or outpouching of the remaining aortic wall. The abdomen was closed, and the animal was allowed to recover.

Two weeks later, abdominal angiography was repeated via a femoral arteriotomy. Since no definite aneurysm was identified in any dog at this time, the catheter used for contrast material injection was exchanged for a 9-F angioplasty balloon catheter (Medi-tech, Watertown, Mass) and the balloon (2 cm in diameter and 3 cm long) was positioned in the aorta at the level where surgery had been performed. The balloon was gently inflated (four times) until the aorta became de-

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formed (ie, there was asymmetric bulging at the site of the previous surgery). Inflation pressure ranged from 1.8 to 2.3 atm, and each dilation lasted for 1 minute. This procedure was similar to that used by Zollikofer et al (13) to create experimental aortic aneurysms in dogs. Two weeks after dilation, aneurysm formation was documented angiographically immediately before graft placement.

Graft Placement and Follow-up

The aneurysm was located on the angiogram by means of bone landmarks. A 12-F Teflon catheter was then inserted through a femoral (four dogs) or carotid (two dogs) arteriotomy site and advanced across the aneurysm. The nylon-covered graft, which had been sterilized with ethylene oxide, was carefully compressed and advanced through the catheter with a blunt-tipped, 8-F introducer wire. When the nylon-covered portion of the graft had bridged the aneurysm, the introducer wire was held tight and the catheter was slowly withdrawn, releasing the graft and allowing it to expand. Once the graft was deployed, it could not be repositioned or retrieved. Therefore, it was essential to locate the aneurysm exactly and bridge it completely with the nylon-covered portion of the graft.

Except for systemic heparinization prior to all angiography, the dogs received no anticoagulation therapy during the follow-up period. An angiogram was obtained 2 weeks after graft placement and again at the end of the follow-up period. The dogs were killed by exsanguination under deep sodium pentobarbital anesthesia after 2 days (one dog), 1 month (one dog), 5 months (one dog), 6 months (two dogs), and 7 months (one dog). The entire abdominal aorta, including both kidneys and renal arteries, was collected en bloc, and all specimens were examined grossly and microscopically.

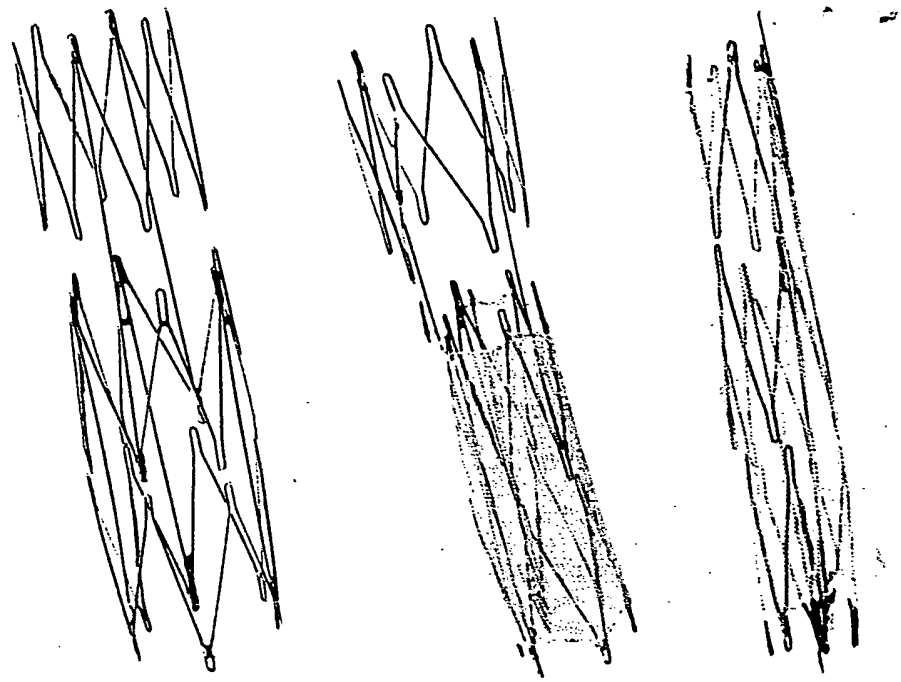


Figure 1. Construction of self-expanding arterial endovascular graft. (a) Graft framework, consisting of three self-expanding metallic zigzag stents connected in tandem. The stents are constructed from 0.016-inch (0.4-mm) stainless steel wire. (b) Completed graft. The lower two stents are covered with nylon. The noncovered lead stent anchors the graft within the aneurysm. (c) Barbs made of 0.014-inch (0.3-mm) stainless steel wire have been attached at both ends to anchor this graft.

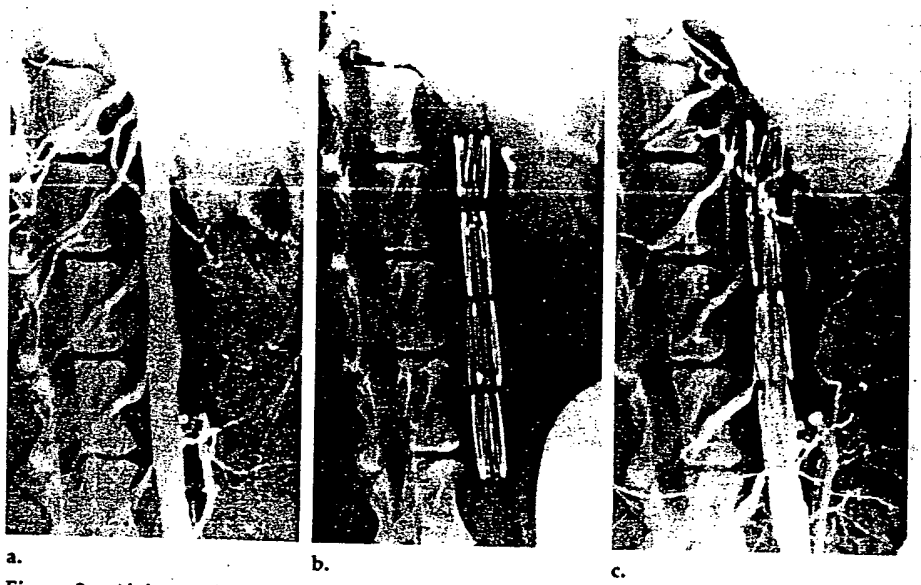


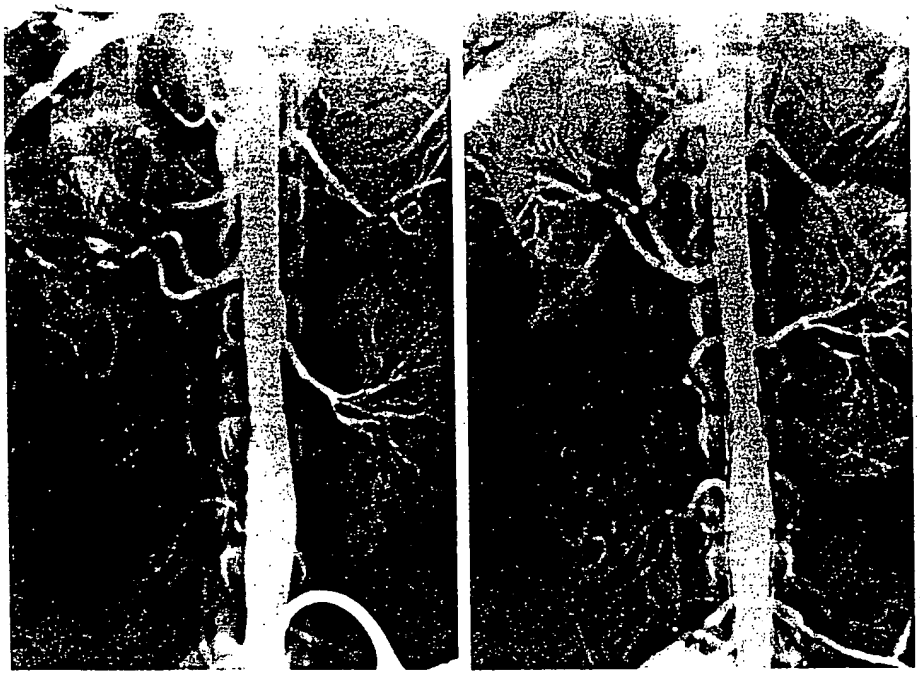
Figure 2. Abdominal radiographs of aneurysm and graft. (a) Lateral aortogram demonstrates an experimentally created, 5-mm, sacculated infrarenal aneurysm of the abdominal aorta. (b) Radiograph obtained immediately after placement of the graft across the aneurysm. Fabric covers the three distal stents. (c) Aortogram obtained 6 months after graft placement. The aortic lumen now appears normal, and side branches covered by the graft are patent.

RESULTS

Aneurysms developed after balloon dilation in all six dogs. At angiography, these averaged 3 cm in length (range, 2–5 cm) and increased the original aortic diameter by 46% (range, 36%–58%). In all cases, the endovascular graft was successfully placed across the aneurysm (Figs 2–4).

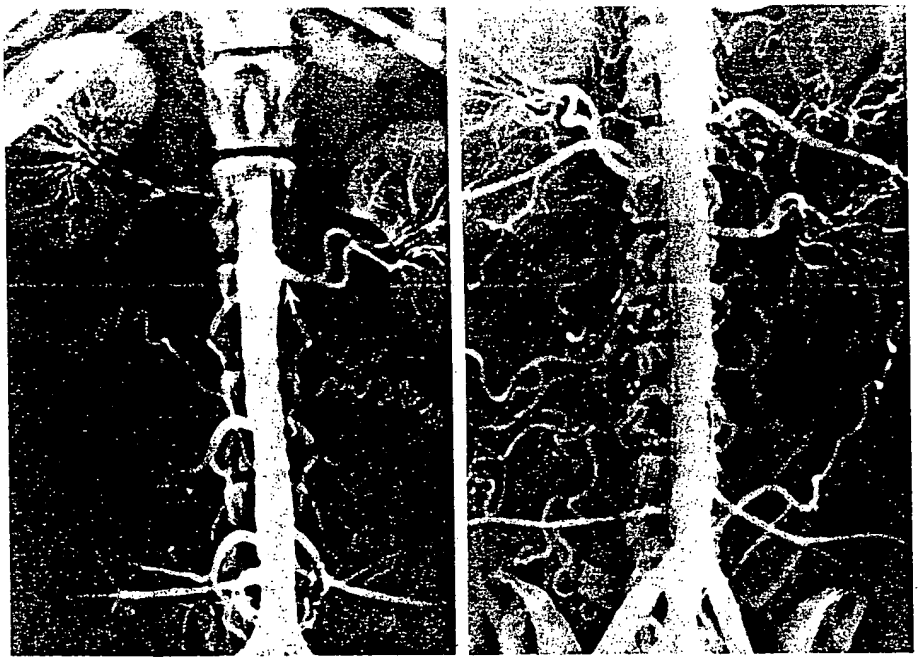
In five of the six dogs, aortography before death demonstrated patency of the graft and the side branches covered by the nylon (Figs 2c, 3b, 4b). The aortic lumen appeared normal on these aortograms, except in one dog that had minimal (<1-mm) residual aortic dilatation at the site of the aneurysm 7 months after graft placement (Fig 3b). There was no evidence of graft migration or of vascular narrowing or perforation in any of these five animals. In one dog, the left renal artery orifice was slightly narrowed at one point after balloon dilation (Fig. 4a). However, the artery remained patent after graft placement, even though the nylon completely covered the vascular origin. The artery appeared normal at angiography at 6 months, even though chronic ischemic changes were present in the left kidney at histologic examination. Specifically, the left renal cortex exhibited moderate, diffuse atrophy.

The remaining dog in this study



a. b.

Figure 3. Minimal residual dilatation at aneurysm site. (a) Aortogram demonstrates a large fusiform aneurysm at the L-4 level. (b) Seven months later, final aortogram shows dilatation of less than 1 mm at the L-4 level. Side branches are patent.



a. b.

Figure 4. Sacculated aneurysm at origin of left renal artery. (a) Slight narrowing at origin following balloon dilation (arrow). (b) Follow-up aortogram obtained 6 months after graft placement shows a normal-appearing left renal artery, even though the arterial orifice was covered by the fabric portion of the graft.

was found comatose 2 days after graft placement. The creatinine level had risen to 8.5 mg/dL (751 μmol/L). An abdominal aortogram showed incomplete expansion of the caudal end of the graft, luminal narrowing in this region, and nonvisualization of the renal arteries. In addition, the graft had migrated 0.5 cm cephalad, and the nylon portion covered the origin of both renal arteries. This dog was one of those in which a noncovered lead stent had been used as an anchor. No graft migration was noted in the other four dogs in which that design was used.

At necropsy, scar tissue was found around the aorta at the surgical site in the five dogs followed up for at least 4 weeks. The aorta was opened longitudinally in all these dogs, and a thin, translucent membrane covered each graft (Fig 5). No gross narrowing of the aorta was noted in any animal. The aneurysm in each of these dogs was bridged and effectively excluded by a new vascular lumen that had formed within the graft and was continuous with the native aorta.

Microscopically, the dog killed 48 hours after graft placement exhibited acute, necrotizing panarteritis involving approximately 30% of the aortic mural circumference. The damage was characterized by segmental loss of the intima and a portion of the media. The subjacent media contained hemorrhage and necrosis, as did the adventitia, which also exhibited acute inflammation. Thrombosis and perivascular inflammation and necrosis were found associated with the adventitial arterioles. These acute vascular changes are similar to those reported by Zollikofer et al (13). In the dogs followed up for at least 4 weeks, the endovascular grafts were covered with neointima (Fig 6), but the material remained porous at the origin of aortic side branches. Neointima was present on the fabric fibers in the areas where they crossed the vessel orifices, which produced minimal narrowing. In the region of the aneurysm, a proliferation of granulation and connective tissues was found between the endovascular graft and the aortic wall (Fig 6).

DISCUSSION

Abdominal aortic aneurysms are identified in 1%–2% of patients undergoing aortoiliac angiography (14,15). More than 90% are secondary to atherosclerosis, and 89% are located in the infrarenal aorta (16–18). Men are affected more frequently than women (5:1), and most patients are 60 years of age or older (16–18).

Darling et al (19) demonstrated that 25% of patients with abdominal aortic aneurysms who did not undergo corrective surgery died of ruptured aneurysm, and this percentage doubled when the diameter of the aneurysm exceeded 7.0 cm. Surgical mortality in younger, asymptomatic patients undergoing elective resection is 2%–5%, but it may reach 20% in older, symptomatic patients and is 50%–60% if the aneurysm has ruptured (14).

Research in our laboratory has been directed toward developing a less invasive alternative for the management of aortic aneurysm. Initially,

self-expanding Gianturco stents were covered with Dacron to form an endovascular graft for transcatheter placement (11). However, the Dacron was not expandable and had a tendency to wrinkle, promote thrombosis or fibrogenesis, and eventually narrow the lumen. Also, side branches covered by the Dacron became occluded.

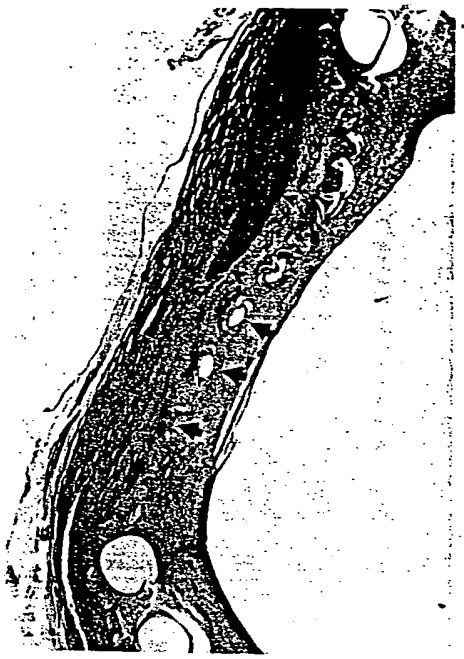
Recently, Yoshioka et al (10) from our laboratory placed self-expanding stents covered with expandable nylon in the normal dog aorta. These grafts were tolerated very well by the animals, and a lamellar neointima developed on the fabric surface and around the stent wires, without irregular thickening, folds, luminal narrowing, or side branch occlusion.

Nylon is unique among the materials tested in this context because it stretches neatly around the stent, conforming to the normal lumen. It can also provide a framework for neointimal encasement, which leads to the formation of a vascular lumen bounded by a new, reinforced wall that should be stronger than that of the aneurysm. This neoluminal formation was seen in the dogs followed up for 4 weeks or longer. In each of these animals, the endovascular graft conformed to the aortic wall above and below the aneurysm, effectively excluding the aneurysm and enabling reconstitution of the normal lumen.

Microscopically, neointima was found on the fabric strands bridging side branch orifices, which indicates that these vessels may eventually have been occluded. Yoshioka et al (10) attributed prolonged patency to the porous nature of the stretched fabric and to the high pressure and flow rate in the aorta. The prolonged patency of aortic side branches covered by the nylon graft may or may not be advantageous. It should allow ample time for collateral vessel formation, thereby preventing damage to tissues supplied by the occluding side branches (ie, the native aortic wall). However, preservation of side branches may promote continued expansion of the aneurysm through transmission of radial forces. Additional research with a model that more closely approximates the clinical situation is needed to resolve the question of maintaining patent side branches for extended periods of time.

One dog was killed 2 days after a graft was placed across a sacculated aneurysm located at the level of the left renal artery. Initially, only the orifice of the left renal artery was covered by the fabric, but within 48 hours of placement the graft migrated 0.5 cm cephalad, so that both renal arteries were covered by the nylon. More important, the distal end of the graft failed to expand completely because one of the distal bends in the stent wire became entangled in the fabric, possibly during insertion of the graft into the delivery catheter. The incomplete expansion most likely resulted in increased turbulence and decreased blood flow through the graft, which promoted significant thrombus formation on the nylon and led to the occlusion of both renal arteries.

5.



6.

Figures 5, 6. (5) Photograph of bisected aorta 6 months after placement of an endovascular graft. A thin, translucent membrane (neointima) covers the graft. (6) Histologic cross section of the aorta at the level of the aneurysm. Absence of internal elastic lamina (arrowheads) indicates site of previous surgery. Granulation and connective tissues have proliferated and filled in the region of the aneurysm (ie, between the graft and the remaining aortic wall). Neointima surrounds the individual fibers of the fabric (arrows). The stent wire was removed for slide preparation; large discrete spaces indicate where it was located (Verhoeff-Van Gieson stain; original magnification, ×60).

Covering the renal artery orifices with the fabric portion of a properly expanded graft should not produce renal artery thrombosis (10). In this study, the origin of the left renal artery in one of the dogs was completely covered by the fabric portion of the graft, but at angiography the artery was patent and appeared normal after 6 months. However, moderate, diffuse cortical atrophy was noted at histologic examination in the kidney and was presumably due to ischemia. Therefore, the presence of the fabric was probably a contributing factor. Further research is needed to evaluate renal function when the orifices of the renal arteries are covered by the fabric portion of the graft. In humans, most abdominal aortic aneurysms are located below the renal arteries, and covering the renal arteries with the fabric portion of the graft would not be necessary.

Grafts that conformed to the aortic lumen above and below the aneurysm were tolerated very well by the dogs, for as long as 7 months. However, the grafts must be properly placed and well anchored. Migration of the one graft that failed may have been prevented by equipping the lead stent with barbs. This postulation is supported by the previous work with the graft in normal vessels (10). However, anchoring barbs may be useful only when at least one segment of normal vascular wall is present, such as in sacculated aneurysms and at either end of fusiform defects.

The large size of the endovascular graft delivery system (12 F) was the most significant technical disadvantage. Again using 0.016-inch wire, we have recently constructed stents with five bends at each end that have an expaned diameter similar to that in stents with six bends. A completed graft comprising the five-bend stents connected in tandem and covered with nylon will pass through a 9-F

Teflon sheath. However, the efficacy of this new design has yet to be determined.

In conclusion, expandable nylon graft material supported by self-expanding Gianturco stents acts as a framework for neointimal encasement and the formation of a new vascular lumen, allowing effective exclusion of sacculated aneurysms in the infrarenal aorta in dogs. These endovascular grafts can be placed percutaneously through a catheter, obviating the need for general anesthesia and major surgery. The technique could eventually enable a significant reduction in the morbidity and mortality associated with current methods of correction. However, there were many variables and few animals in this feasibility study, and these limitations emphasize the need for significantly more research. Along with the porous nature of the graft material, the basic serial histologic changes in the animal model need to be better understood. ■

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